IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 2, December 2025
Impact Factor: 7.67

A Review on Nasopulmonary Drug Delivery System

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Abstract: *Nasal and nasopulmonary drug delivery have gained increasing attention as convenient, reliable, and promising routes for systemic drug administration. Their advantages include high vascularity, large surface area, rapid absorption, and the avoidance of hepatic first-pass and gastrointestinal metabolism. Despite these benefits, the design of effective nasopulmonary drug delivery systems (NPDS) remains challenging. Critical factors such as particle size, shape, surface properties, and stealth characteristics significantly influence the ability of nano and microparticles to reach targeted sites within the respiratory tract. NPDS offer notable potential for treating a wide range of conditions, including allergies, respiratory disorders, and central nervous system diseases that require rapid or targeted drug delivery, such as Parkinson's and Alzheimer's diseases. Various device strategies ranging from sprays and drops to gels and solid formulations are being explored to enhance drug deposition, retention, and therapeutic efficiency. Optimizing these systems is essential for improving safety, patient compliance, and overall clinical outcomes..*

Keywords: Naso-Pulmonary drug delivery, Mucociliary clearance, Nasal, Pulmonary, Respiratory tract

I. INTRODUCTION

The nasal route has been utilized for therapeutic purposes since ancient times, particularly in the Indian Ayurvedic system, where the practice known as *Nasya* involved administering medicaments through the nose. In modern pharmaceutics, intranasal and nasopulmonary drug delivery have emerged as reliable and efficient alternatives to oral and parenteral administration. This route has long been used for the relief, prevention, and treatment of various nasal disorders, but its scope has expanded significantly due to its unique physiological and pharmacokinetic advantages.Intranasal administration offers both local and systemic effects, allowing drugs to be delivered directly to the nasal mucosa or absorbed into systemic circulation. It is especially beneficial for molecules with poor oral bioavailability, including peptides, proteins, and hydrophilic drugs. Importantly, the intranasal route provides a non-invasive pathway to bypass the blood–brain barrier, enabling direct delivery of CNS-active compounds. Similarly, pulmonary delivery via inhalation ensures rapid drug absorption due to the lung's large surface area, thin epithelial barrier, and rich vascularization, making it valuable for respiratory diseases such as asthma and COPD.

The growing interest in nasopulmonary drug delivery systems (NPPDS) is driven by the need for rapid onset of action, improved patient compliance, and avoidance of first-pass metabolism. Devices such as nasal sprays, inhalers, drops, gels, and powder-based systems are widely explored for delivering medications ranging from decongestants and migraine treatments to hormone replacement therapies. Despite its advantages, nasal drug delivery faces challenges, particularly limited residence time and insufficient contact between formulations and the nasal mucosa.Understanding nasal anatomy is essential for optimizing drug absorption. The nasal cavity, divided into two chambers by the septum, has an approximate surface area of 75 cm² and consists of vestibular, respiratory, and olfactory regions. The respiratory region lined with ciliated and non-ciliated columnar cells, goblet cells, and approximately 300 microvilli per cell plays the most significant role in systemic drug delivery. Its high permeability and vascularity make it an attractive target for

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researchers aiming to enhance drug transport, prolong mucosal residence, and develop effective nasopulmonary drug delivery systems.

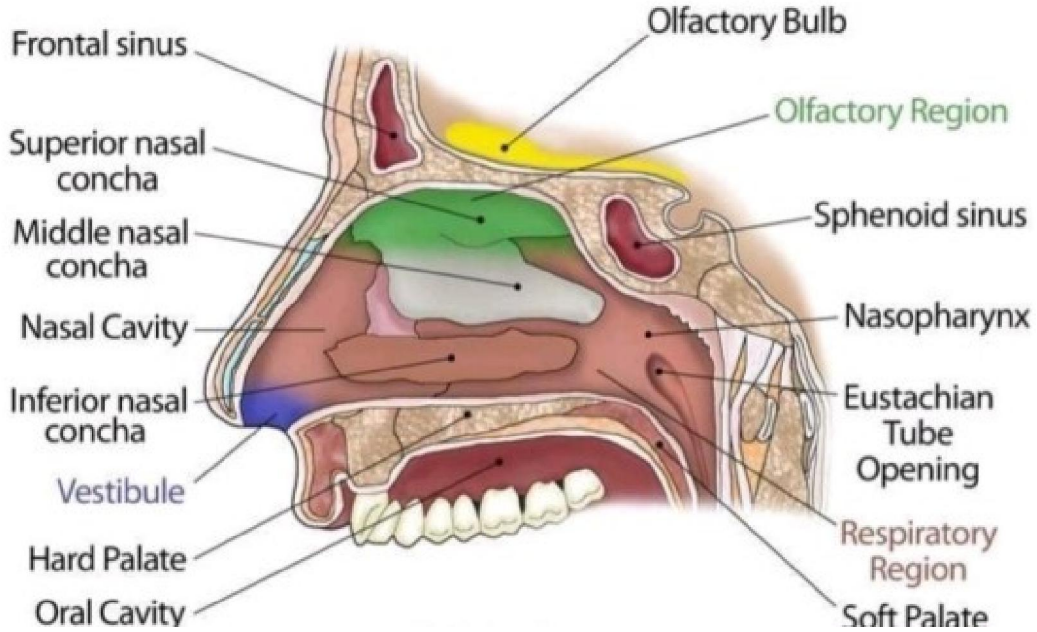

Figure: Anatomy and Physiology of Nasal

ADVANTAGES:

Intranasal Delivery:

- Bypasses blood-brain barrier
- Suitable for CNS-active compounds
- Ideal for poor oral bioavailability compounds

Pulmonary Delivery:

- Rapid absorption, Good blood supply
- Large absorptive area (up to 100m²),Thin mucosal membranes (0.1 µm)
- Suitable for respiratory diseases (asthma, COPD),Requires permeation enhancers for large macromolecules

DISADVANTAGES

- Pathological conditions such as allergies and cold may alert significantly the nasal bioavailability
- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet early established.
- Relative inconvenient to patient when compared to oral delivery systems since they possibility of some irritation.

Anatomy and Physiology of the Nose and Pulmonary System

The nasal cavity plays a crucial role in respiration, filtration, humidification, and drug absorption. It is divided into three primary regions, each with distinct structural and functional characteristics important for effective nasopulmonary drug delivery.

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1. Nasal Vestibule

The nasal vestibule is the anterior-most part of the nasal cavity. It is lined with keratinized stratified squamous epithelium and contains vibrissae (nasal hairs), which act as a primary filtration barrier against dust and particulate matter.

2. Respiratory Region

The respiratory region is the largest and most significant area for drug absorption. It is lined with pseudostratified ciliated columnar epithelium containing goblet cells responsible for mucus secretion.

Approximately 15–20% of the respiratory epithelial cells are covered by long cilia measuring 2–4 μm in length.

These cilia facilitate mucociliary clearance, transporting mucus and entrapped particles toward the nasopharynx.

This region provides a large surface area and rich vascularization, making it a major site for systemic drug absorption.

3. Olfactory Region

The olfactory region is located at the roof of the nasal cavity and covers a small area of about 10 cm^2.

It contains olfactory neurons that provide a direct connection to the central nervous system.

This anatomical feature allows certain drugs to bypass the blood–brain barrier and reach the cerebrospinal fluid.

Physiological Characteristics Relevant to Drug Delivery

pH of Nasal Secretions:

Adults: 5.5 – 6.5

Infants and young children**: 5.0 – 6.7**

Mucosal Membrane: The entire nasal cavity is lined with a mucous membrane that supports drug dissolution and absorption.

Composition of Nasal Mucus:

- 95% water
- 2% mucin
- 1% salts
- 1% proteins (including albumin, lysozyme, lactoferrin)
- 1% lipids

Evaluation of Nasopulmonary Drug Delivery Systems

A comprehensive evaluation of nasopulmonary drug delivery systems (NDDS) is essential to determine their safety, efficacy, and clinical suitability. Assessment begins with analyzing the physicochemical properties of the formulation to ensure optimal aerosolization and deposition within the respiratory tract. Techniques such as cascade impaction are commonly used to determine aerodynamic behavior and particle size distribution critical factors influencing lung penetration and deposition efficiency.Preclinical studies assess pharmacokinetic and pharmacodynamic characteristics using suitable animal models. These studies evaluate systemic absorption, tissue distribution, drug clearance, and overall therapeutic potential following nasal or pulmonary administration. Additionally, disease-specific models provide insight into the effectiveness of NDDS in relevant pathological conditions.

Clinical studies play a pivotal role in validating NDDS for human use. Pharmacokinetic evaluations determine drug absorption, bioavailability, and systemic exposure, while clinical efficacy trials measure therapeutic outcomes in patient populations. Safety assessments monitor potential adverse effects related to nasal or pulmonary delivery. Patient-centered usability studies further determine the acceptability, convenience, and compliance associated with NDDS.

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Table : Evaluation Parameters of Nasopulmonary Drug Delivery Systems

Parameter	Description	Procedure	Equation
Fine Particle Fraction (FPF)	Represents the proportion of particles reaching the lower airways with an aerodynamic diameter < 5 µm, which have a higher chance of deep lung deposition.	Calculated from APSD (Aerodynamic Particle Size Distribution) data.	**FPF (%) = (Mass of particles < 5 µm / Total mass of particles) × 100**
Emitted Dose (ED)	Total quantity of drug discharged from the device.	Measured using gravimetric analysis or a dose-collection chamber.	**ED = Mass of drug collected / Number of actuations**
Delivered Dose (DD)	Represents the amount of drug entering the patient's lungs.	Determined using in vivo studies or breathing simulation models.	**DD = Mass of drug deposited in lungs / Number of actuations**
Drug Content Uniformity (DCU)	Evaluates uniformity of drug content in each dose.	Measured using analytical techniques such as HPLC.	**DCU (%) = (Standard deviation of drug content / Mean drug content) × 100**
In Vivo–In Vitro Correlation (IVIVC)	Demonstrates correlation between pharmacokinetic properties and in vitro performance parameters (e.g., FPF, APSD).	Statistical analysis of in vivo and in vitro data.	—

Table :Recent Study on Nasopulmonary Drug Delivery Systems

Topic / Study (Title)	Authors	Journal & Year	Key conclusions / Findings
The Comprehensive Review: Exploring Future Potential of Nasopulmonary Drug Delivery Systems for Nasal Route Drug Administration	Rahul Pal, Prachi Pandey, ManjuKoli, Khushi Srivastava, Vaisanavi Tiwari, Aman Kumar Gaur, Prottay Dutta	Journal of Drug Delivery & Therapeutics, 2024	This review summarizes the advantages of nasopulmonary delivery (rapid absorption, avoidance of first-pass metabolism, noninvasive use), describes nasal anatomy & physiology, and analyzes different delivery forms (sprays, powders, gels). It discusses limitations (e.g., mucociliary clearance, formulation challenges) and calls for further research to optimize efficacy and safety.
Nanomedicines for targeted pulmonary delivery: receptor-mediated strategy and alternatives	W. Wang, Z. Zhong, T. N. Hiew, Y. Huang, C. Wu & X. Pan	Nanoscale, 2024	This mini-review highlights that nanomedicine-based pulmonary delivery (PDTNs) can achieve targeted drug accumulation in lung lesions (e.g., lung cancer, infection, inflammation) and reduce systemic side effects. Strategies include receptor-mediated targeting, mucus-penetrating designs, stimulus-responsive systems, and magnetic-driven targeting
Nanoparticle-Based Drug Delivery Systems in Inhaled Therapy: Improving Respiratory Medicine	Z. Huang	Pharmaceuticals, 2024	The article reviews recent advances in inhaled nanoparticle therapies, allowing delivery of diverse drugs while avoiding systemic clearance. Nanoparticles enhance local drug concentration in lungs and reduce systemic side effects.
Inhaled biologics for respiratory diseases:	S. Lobo	Drug Delivery and Translational	This 2025 review reports that pulmonary delivery (via pMDIs, DPIs, nebulizers) is increasingly

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clinical potential and emerging technologies		Research, 2025	effective not only for small-molecule drugs but also for complex biologics. Pulmonary route offers rapid therapeutic action, high local concentration in lungs, minimized systemic exposure, and improved patient adherence.
Intranasal Delivery: Formulation Factors and Insights Into User Experience	Z. Xi, D. Das, et al.	AAPS PharmSciTech, 2025	This recent study focuses on formulation- and user-related factors influencing intranasal delivery, including taste/bitterness, patient acceptability, and compliance. It underlines that formulation attributes (pH, excipients, device design) significantly affect usability and therapeutic success.

Potential Applications of Nasopulmonary Drug Delivery Systems

Nasopulmonary drug delivery systems (NDDS) offer a versatile platform for targeted and systemic therapeutic applications. Due to their ability to deposit drugs directly in the nasal cavity or lungs, NDDS are particularly useful for managing upper and lower respiratory disorders. Additionally, their capacity for rapid systemic absorption makes them ideal for drugs requiring quick onset of action or those with poor oral bioavailability.

1. Local Delivery to the Nose and Lungs: Drug can deliver drugs locally to treat conditions such as:

Asthma
Chronic Obstructive Pulmonary Disease (COPD)
Allergic rhinitis
Respiratory tract infections

2. Systemic Drug Delivery

Drug absorption through nasal or pulmonary mucosa allows systemic delivery without first-pass metabolism. This is particularly beneficial for:

Peptides and proteins
Hormones
Vaccines
Analgesics

3. Delivery to the Brain

The nasal route provides a direct connection to the central nervous system via the olfactory and trigeminal pathways. NDDS are being explored for treating:

Parkinson's disease
Alzheimer's disease
Brain tumors

Treatment of Nasopulmonary Disorders

NDDS represent a modern and efficient method for treating respiratory diseases by delivering drugs directly to the nasal cavity or lungs.

1. Asthma

NDDS are widely used to administer:

Bronchodilators
Corticosteroids
Anti-inflammatory.

2. Chronic Obstructive Pulmonary Disease (COPD)

NDDS deliver bronchodilators and adjunct therapies directly into the lungs. They enhance lung function and improve quality of life by ensuring efficient drug deposition.

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3. Cystic Fibrosis

NDDS are used to administer:

Antibiotics

Mucolytics

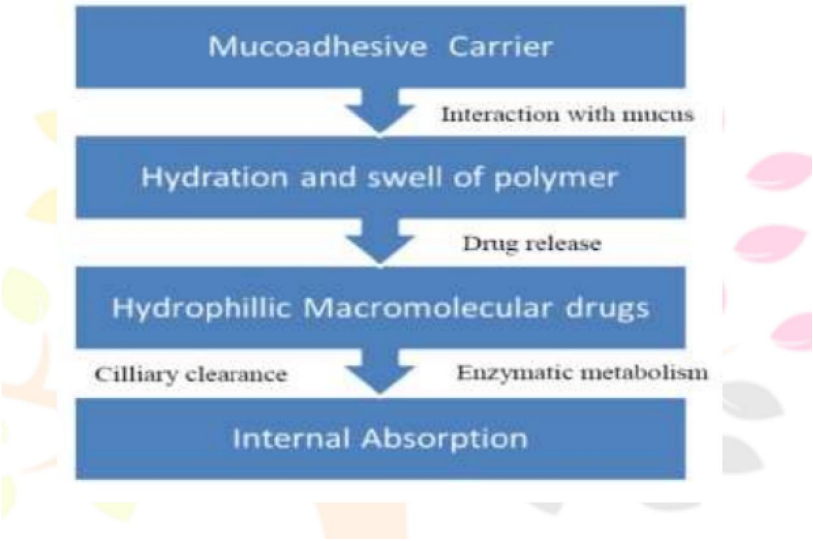
These systems improve lung function and reduce exacerbation frequency in cystic fibrosis patients.

4. Lung Cancer

Research is ongoing into inhalable chemotherapeutic agents delivered via NDDS. This approach may reduce systemic toxicity and enhance drug concentration at the tumor site.

MECHANISM OF DRUG ABSORPTION IN THE NASOPULMONARY DRUD DELIVERY SYSTEM

Two mechanisms have been considered generally out of several mechanisms that have been proposed.The first involves an aqueous route of transport, which is also known as the paracellular route.



Key feature of this mechanism involves

This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for a drug with a molecular weight greater than 1000 Daltons.The second involves transport through a lipoidal route is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport. Paracellular (intercellular) : slow and passive absorption of peptides and proteins associated with intercellular and tight junctions.

Transcellular(intracellular) : Transport of lipophilic drugs passive /Active diffusion Transcytotic : particle taken into a vesicles and transferred to the cell.

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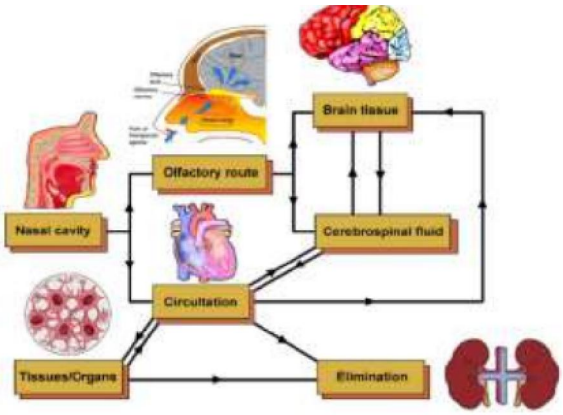

Figure: Pathways for drug delivery via nasal route

II. RESULTS AND DISCUSSION

The review highlights that nasopulmonary routes offer distinct advantages such as avoidance of first-pass metabolism, rapid systemic absorption, and suitability for biopharmaceuticals with low oral bioavailability. The anatomy of the nasal cavity—particularly the vascular and ciliated respiratory region—plays a central role in enhancing drug uptake. However, mucociliary clearance and limited residence time remain major barriers, necessitating the use of mucoadhesive polymers, viscosity enhancers, and particulate carriers to improve retention.Evaluation parameters such as **Fine Particle Fraction (FPF)**, **Emitted Dose (ED)**, **Delivered Dose (DD)**, and **Drug Content Uniformity (DCU)** provide essential insights into aerosol performance and formulation quality. Recent studies also emphasize the need for IVIVC models to predict therapeutic outcomes more reliably.

Research findings show that NDDS are effective for managing asthma, COPD, cystic fibrosis, and infectious diseases by targeting drugs directly to the respiratory tract. In addition, intranasal delivery provides a unique pathway to the central nervous system, enabling treatments for neurological disorders without invasive procedures.Recent literature demonstrates increasing interest in nanomedicines, inhaled biologics, and receptor-targeted pulmonary delivery systems. These approaches enhance drug deposition, improve bioavailability, and reduce systemic toxicity compared to conventional delivery methods. However, challenges such as variability in nasal physiology, formulation instability, and long-term safety concerns of enhancers and nanoparticles require further investigation.

III. FUTURE SCOPE

Nasopulmonary drug delivery systems (NDDS) represent a rapidly advancing field with significant potential for innovation in both local and systemic therapy. Future research is expected to focus on the development of **advanced nano-carriers**—such as mucus-penetrating nanoparticles, ligand-targeted systems, and stimuli-responsive formulations—to improve drug retention, absorption, and targeting within the nasal cavity and lungs. Novel biomaterials like chitosan derivatives, thiolated polymers, and smart hydrogels may be engineered to enhance mucoadhesion and open epithelial tight junctions, thereby improving the delivery of peptides, proteins, nucleic acids, and vaccines.

The **nose-to-brain delivery pathway** remains a promising target for treating neurodegenerative diseases such as Parkinson's, Alzheimer's, and brain tumors. Significant advancements are anticipated in intranasal delivery of biologics, gene therapy vectors, and nanocarriers capable of bypassing the blood–brain barrier. Additionally, innovations in **device technology**, including smart inhalers, breath-actuated nasal devices, and 3D-printed delivery systems, will likely improve dosing accuracy and patient compliance.Future work should also emphasize **in vitro–in vivo correlation (IVIVC)** models, computational lung deposition modeling, and patient-specific therapy optimization. Regulatory acceptance and long-term toxicity studies of permeation enhancers and nanocarriers will be critical. Overall, NDDS will continue to evolve toward **personalized, targeted, and minimally invasive therapeutic platforms**.

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IV. CONCLUSION

Nasopulmonary drug delivery systems have emerged as effective, noninvasive platforms for delivering a wide range of therapeutic agents, including small molecules, peptides, proteins, biologics, and neuroactive compounds. Their inherent physiological advantages—large surface area, rich vascularization, rapid drug absorption, and ability to bypass the blood–brain barrier—make them suitable for both local respiratory treatments and systemic drug delivery.The review demonstrates that formulation factors such as particle size, shape, mucoadhesion, surface characteristics, and device selection are crucial for successful drug deposition and absorption. Although NDDS provide promising solutions for treating respiratory diseases, neurological disorders, and systemic conditions, certain limitations such as mucociliary clearance, nasal irritation, and inconsistent absorption pose challenges.Advancements in nanotechnology, polymer science, and device engineering continue to improve the effectiveness, safety, and patient usability of NDDS. With ongoing research, nasopulmonary delivery is expected to evolve into a highly precise and patient-friendly therapeutic approach, offering substantial benefits in future pharmaceutical and clinical applications.

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